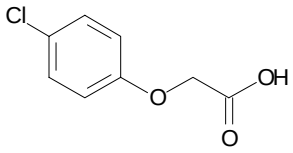
Appendix B:
Toxicity Studies with 4-chlorophenoxyacetic acid (4-CPA) and Structures Related to 4-CPA.

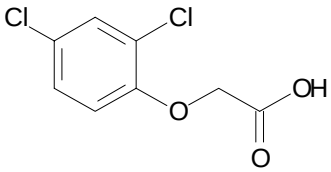
Structure of 4-chlorophenoxyacetic acid (4-CPA) (PC 019401)



The following are brief summaries of the cancer findings for each of the structural analogs for which there are studies. In some cases the Cancer Assessment Review Committee (CARC) has not evaluated the pesticide. Comparison of the results from toxicity studies are made for 4-CPA and the four analogs, 2,4-dichlorophenoxyacetic acid, 2-methyl-4-chlorophenoxyacetic acid, 3-chlorophenoxy-2-propionic acid, and 2-methyl-4-chlorophenoxybutyric acid (Table 1). More structurally remote chlorophenoxy acid pesticides are: (1) 2,4-dichlorophenoxybutyric (not carcinogenic in rats or mice), (2) 2,4-dichlorophenoxy-2-propionic acid (not carcinogenic in rats or mice), (3) 2,4,5-trichlorophenoxyacetic acid (evidence of carcinogenicity in total tumors in female mice, but not rats), and (4) 2,4,5-trichlorophenoxy-2-propionic acid (no studies available). These latter pesticides are not shown and not summarized further. [Information from Carcinogenicity Peer Review (4th) of 2,4-D, 1/29/97.]

Although there are no carcinogenicity studies on 4-CPA, the weight of the evidence does not suggest that 4-CPA would be carcinogenic in life-time studies at reasonable doses not causing excessive toxicity.

Structure of 2,4-dichlorophenoxyacetic acid (2,4-D)(PC 030001)



The following is a summary of the findings from the fourth and last cancer assessment of 2,4-D. This pesticide has the largest toxicity data base of all the analogs. The Cancer Peer Review Committee (CPRC) concluded that 2,4-D should remain classified as a "Group D" - Not classifiable as to a human carcinogenicity. That is, the evidence is inadequate and cannot be interpreted as showing either the presence or the absence of a carcinogenic effect.

2,4-D was initially classified as a possible human carcinogen, based on a significant increased trend for brain astrocytomas in male Fisher 344 rats and suggestive to weak and conflicting evidence of non-Hodgkin's lymphoma from several epidemiological studies. There was no evidence of tumor induction in female rats or male or female B6C3F1 mice, however, the CPRC concluded that the highest dose tested in both studies was sufficiently toxic to adequately test for carcinogenicity. Repeat studies were conducted in rats and mice at adequate doses, but neither study showed statistically significantly increased tumor incidence in either species or sex.

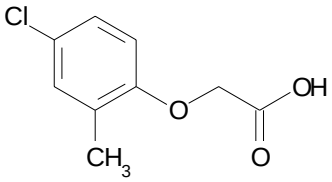
Mutagenicity studies showed consistently negative results without activation and positive and negative result with activation. The CPRC concluded that although cytogenic activity was seen, there was no concern for mutagenicity.

Metabolism studies in the rat indicated that 85 to 94% of the parent was excreted unchanged in the urine with 0% -1.3% of 2 uncharacterized compounds and 4 to 10% was excreted as the parent in feces. Total excretion (98 to 99.5%) occurred within 48 hours.

The CPRC and SAP agreed on a "Group D" classification.

[Information from Carcinogenicity Peer Review (4^{th}) of 2,4-D, 1/29/97.]

Structure and results on 2-methyl-4-chlorophenoxyacetic acid (MCPA) (PC 030501)



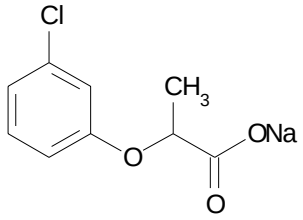
MCPA has not been reviewed by the CARC, but a toxicology reviewer indicated that no dose related tumors were seen in rats or mice at adequate doses to test for carcinogenicity.

A battery of mutagenicity studies shows a positive study for chromosomal aberrations in human lymphocyte cells and weakly mutagenic response in an *in vivo* sister chromatid exchange study. The remaining 6 *in vivo* and *in vitro* mutagenicity studies conducted were negative.

The metabolism studies in the rat shows that MCPA is excreted in the urine (74-86%; 53%-69% as the parent and 7-13% as the hydroxymethyl metabolite and 2-5% in the feces). Total excretion occurred within 192 hours (98%).

[Information from the 1-liners and Paul Chin reviewer].

Structure and results on sodium 3-chlorophenoxy-2-propionate (cloprop, sodium salt) (PC 021201)



Life-time carcinogenicity studies have been conducted with cloprop, but there are no definitive conclusions. There was a statistically significantly increasing trend and pair-wise comparison with control for mortality in male and female rats at the top dose. The registrant refused to submit historical control data on morality among the rats used in the carcinogenicity study. Consequently the Peer Review of cloprop was canceled and the pesticide withdrawn.

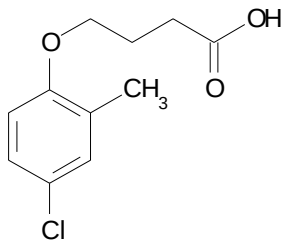
In the mouse study, there was statistically significantly pair-wise comparison of male liver adenomas/carcinomas and male liver carcinomas at the highest dose tested and in females for liver adenomas and carcinomas at the two lowest doses tested, but not at the highest dose tested. One reviewer believed that there was no evidence for carcinogenicity in mice, however another reviewer believed there was evidence of liver cancer in mice. The issue has never been resolved because the pesticide was withdrawn.

Cloprop is negative in a battery of mutagenicity studies.

There are no metabolism studies in rats, but in goats, cloprop is excreted as the parent.

[Information from 1-liners and a memorandum from John Redden.]

Structure and results on 2-methyl-4-chlorophenoxybutryic acid (MCPB) (PC 019201)



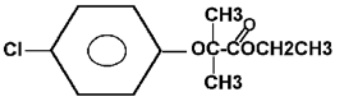
No life-time carcinogenicity studies have been conducted with MCPB.

A battery of mutagenicity studies are negative. One study for chromosomal abnormalities with S9 produced chromosomal abnormalities at high doses.

There are no adequate metabolism studies, but a reference from the literature suggest that bacteria split off acetic acid from the butyric acid residue in plants and cows.

[Information from 1-liners and DERs.]

Structure and results on 2(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester; the Drug Clofibrate (lowers plasma triglycerides and cholesterol)

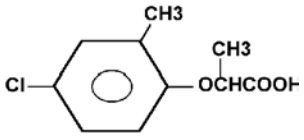


Clofibrate

An International Agency for Research on Cancer (IARC) Monograph on clofibrate states that there is inadequate evidence in humans for carcinogenicity and limited evidence in animals for carcinogenicity.

Clofibrate is peroxisome proliferator and is excreted rapidly in human urine as the parent. (http://193.51.164.11/htdocs/monographs/vol66/clofibrate.html).

Structure and results on mecoprop [2-(2-methyl-4-chlorophenoxy)propionic acid] (PC 031501)



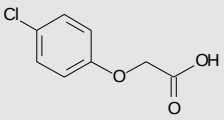
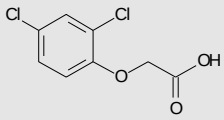
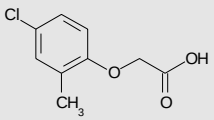
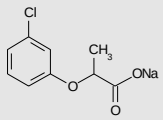
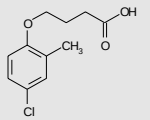
Mecoprop

The acute toxicity of mecoprop is similar to that of 4-CPA. The NOAEL/LOAEL in the rat 90-day feeding study was lower than the NOAEL/LOAEL in rat 90-day neurotoxicity study, which showed no neurotoxic effects, in addition to being lower than 4-CPA in a rat 90-day feeding study. A rabbit developmental toxicity study showed a maternal NOAEL/LOAEL of 30/75 mg/kg/day, but no developmental toxicity at the highest dose tested. The rat developmental toxicity study showed developmental toxicity in the form of decreased crown-rump lengths, decreased ossification of sternebrae and increased intrauterine death at the highest dose tested, which was a maternally toxic dose. The rat developmental effects occurred at a lower dose than the effects from 4-CPA in a rat developmental toxicity study. No 90-day feeding study in dogs is available.

Potential carcinogenic effects have not been fully evaluated as yet, but there is suggestive evidence for increased liver tumors in mice. The rat carcinogenicity study was negative.

A reverse gene mutation study was acceptable and negative and chromosomal aberrations study was acceptable and negative for clastogenicity (MRID# 41013909, TXR# 009589). The remaining mutagenicity studies were unacceptable.

Table 1: Comparison of toxicity studies/results for 4-chlorophenoxyacetic acid (4-CPA) and four analogs of 4-CPA

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)
870.1100 Acute Oral ToxicityLD50	2703 mg/kg	3730mg/kg	3500 mg/kg	1567 mg/kg	1570 mg/kg
870.1200 Acute Dermal Toxicity/LD50	>2000 mg/kg	>2000 mg/kg	>2000mg/kg	-	1000 mg/kg
870.1300 Acute Inhalation Toxicity/LC50	>5.25 mg/L	>1.8 mg/L 4hr	> 6.3 mg/L	-	1.1 mg/L (acetone vehicle)
870.2400 Primary Eye Irritation . .	Severe	Mod/Severe	Mod/Severe	-	Mod/Severe
870.2500 Primary Dermal Irritation	Not irritating	None Irritating	Slight	-	-
870.2600 Dermal Sensitization . . .	Not sensitizing	Not sensitizing	Not sensitizing	-	-
870.3100 Oral Subchronic (rat) . . .	N/L=152/517mkd, Bwt dec & urine volume inc, liver individual cell necrosis	N/L=15/100mkd testes, liver, thyroid weight inc & spleen histop	N/L=50/150ppm N/L=2.5/7.5 mkd inc kidney weight with incr creatinine HDT, no histop	-	N/L=158/-m/k/d HDT palatability noted; kidney weight incr, histop neg
870.3150 Oral Subchronic (dog) . .	N/L=18.6/-mkd HDT (Peer Rev); N/L=3.3/19mkd bwt & food decr; no histop changes seen (DER)	N/L=1.0/3.0 mkd, liver, kidney & testes histo	N/L=0.6/2.4 mkd liver inflammation & clinical chemistry (MCPA-Dimethylamine)	N/L=12.5/50 mkd, bwt decr, liver, kidney & spleen weight incr	N/L=12/40mkd Inc BSP retention, dec spermatogenic activity, prostate & testes tubular atrophy

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	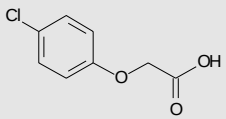	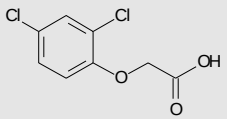	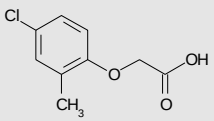	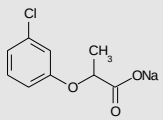	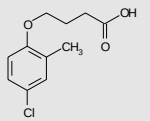
870.3200 21-Day Dermal (rabbit) .	-	N/L= 1000/-mkd	SystN/L=100/1000mkd Mineralization kidney tubules IrritationN/L=	-	-
870.3250 90-Day Dermal	-	-	10/100mkd	-	-
870.3465 90-Day Inhalation	-	-	- -	-	-
870.3700a Developmental Toxicity (rat)	M N/L=150/300mkd Bwt dec & at 1000mkd mortality, tremors & uncoordinated movements D N/L=150/300mkd sternebrae unoss	M N/L=25/75mkd decr Bwt D N/L=25/75mkd, extra rib, dec oss, variations	M N/L=60/120 mkd Bwt D N/L=60/120 mkd Dec Bwt & dec oss	M N/L=400/-mkd HDT D N/L=400/-mkd UA, OPP added; acceptable with rabbit study	M N/L=25/100 mkd,bwt; D N/L=25/100mkd, dec oss
870.3700b Developmental Toxicity (rabbit)	M N/L= 25/–mkd, D N/L=10/25mkd fetal wt dec ascribed to maternal Bwt dec., but unsure of maternal Bwt dec Range-finding (5 rabbits/group) with no control weight. Invalid study, UA	M N/L=30/90mkd ataxia, motor control, dec Bwt D N/L=90/-mkd*	M N/L=30/60 mkd Dec Bwt, food consumption D N/L=60/- mkd	M N/L=100/200 mkd Bwt dec D N/L=100/200mkd Misshapen, compressed & small cerebral hemisphere & compressed cranial nerve & displaced eye	M N/L=5/20mkd, clinical signs, death D N/L=>20/-mkd HDT, NC

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	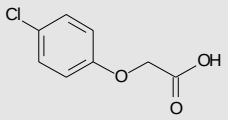	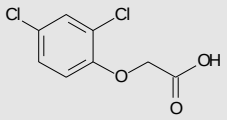	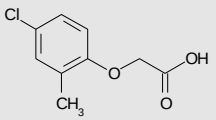	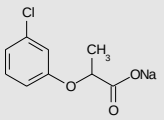	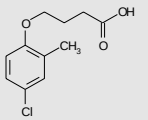
870.3800 Reproduction	[1] (Partly unreadable 1964-5 study) P N/L=12.5/−mkd Studied at too low of dose. No effects in parents or offspring. Since parts unreadable N/L unverifiable UA	P N/L=5/20mkd kidney Off N/L=7.5/20mkd, Bwt dec (same ppm dose as parents)*	P N/L=225/-mkd Off N/L=7.5/225mkd possible pup Bwt dec	P N/L=100/400mkd Off N/L= 100/400mkdec pup Bwt dec	-
870.4100a Chronic Toxicity (rodent)	-	-	-	-	-
870.4100b Chronic Toxicity (dog) .	-	N/L=1/5mkd, liver enzyme inc, histop liver & kidney	N/L=6/30mkd, liver histop & enzyme inc, histop kidneys	-	-
870.4200a Oncogenicity (rat)	-	-	-	-	-
870.4200b Oncogenicity (mouse) . .	-	N/L= 5/62.5 mkd, kidney & adrenal weight inc Inadequate doses No carcinogenicity.	N/L=15.7/79.5mkd histo kidney & wt & calcification No carcinogenicity	N/L=75/300 mkd liver pigmentation Equivocal oncogenicity, UA	-
870.4300 Chronic/Oncogenicity (rat)	-	N/L=5/75mkd, Bwt kidney, liver, liver enz & thyroid changes Not carcinogenicity to equivocal	N/L=1/4.4mkd liver enzyme inc., kidney histop No carcinogenicity	N/L=25/100mkd, liver, kid. need historical control to confirm carcinogenicity, refused submission Not carcinogenic.	-

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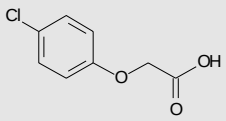
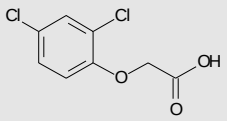
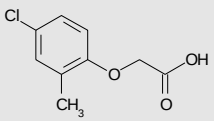
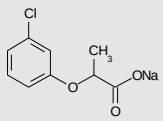
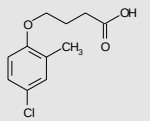
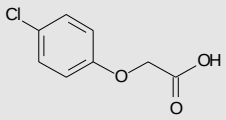
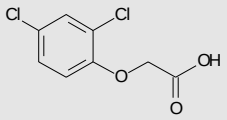
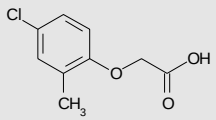
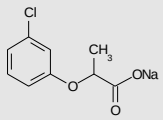
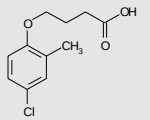
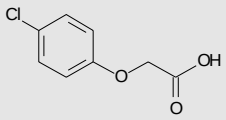
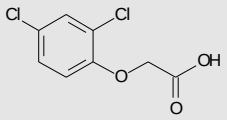
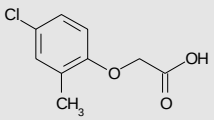
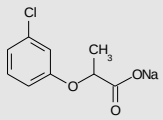
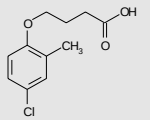
					
870.5100 Mutagenicity—Gene Mutation - bacterial	Neg	Neg	Neg	Neg	Neg
870.5100 Mutagenicity—Gene Mutation - bacterial		Neg	Neg		
870.5300 Mutagenicity—Gene Mutation - mammalian .	Neg	Pos	Neg		Neg
870.5375 Mutagenicity—Structural Chromosomal Aberrations	-	-	-	-	-
Nonguideline Chromosomal aberrations (human lymphocytes).....	-	One pos +/ one neg -	Pos.	-	-
Nonguideline Recom/Convers Assay (Saccharomyces)	-	-	-	Neg	-
Nonguideline Recomb/Convers Assay (Mouse).....	-	-	-	Neg	-
870. 5395 Mutagenicity—Structural Chromosomal Aberrations.	Neg	Neg	Neg	Neg	-
870.5450 Rodent Dominant Lethal	-	-	-	NOAEL>400 mg/kg Neg	-
870.5915 Sister Chromatid Exchange.....	-	Neg +S9/Pos -S9	Weakly Pos.	-	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870.5550 Mutagenicity—Other Genotoxic Effects	-	Neg	-	-	-
870.6100a Acute Delayed Neurotox. (hen)	-	-	-	-	-
870.6100b 90-Day Neurotoxicity (hen)	-	-	-	-	-
870.6200a Acute Neurotox. Screening Battery (rat) . .	-	N/L=67/227mkd altered FOB, dec coordination SystN/L=227/-mkd	N/L=200/400mkd impaired gait males	-	-
870.6200b 90 Day Neuro. Screening Battery (rat)	-	-	N/L=34/177mkd dec motor activity, grip strength, liver histo.	-	-
870.6200 One-year Neuro. Toxicity study (rat)	-	N/L=75/150mkd incr relative forelimb grip strength	-	-	-
870.6300 Develop. Neuro	-	-	-	-	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870.7485 General Metabolism (Lab# 152/517)	-	Excreted as parent in urine (86-94%), 4-11% in the feces Small amounts of metabolites (0.6%-1.3%). 98-99.5% recovered within 48 hr. Excreted mostly un-metabolized	Mostly excreted as MCPA, 7-13% hydroxylated methyl MCPA. 98% excreted within 192 hr. Excreted mostly un-metabolized	Excreted as parent, mostly unmetabolized in the goat UC	Lit.; Bact-Splits off acetic acid from the butyric acid residue in plants and cows UA
870.7600 Dermal Penetration . . .	-	-	-	-	-
Carcogenicity Classification.....	No studies	"D" not classifiable as a human carcinogen	Not likely to be a human carcinogen, but no HIARC or CARC review yet	Rats (historical control required) Chem withdrawn Mice increased pair-wise hepatocellular carcinomas at HDT Unclassified by CARC	No carcinogenicity studies

[1] This 3-generation reproduction study with 4-CPA is reasonably well conducted but the doses were too low (the highest dose tested was 12.5% of the NOAEL from the 90-day subchronic study in rats.). The highest dose tested was 250 ppm and the NOAEL in a 90-day rat study was 2000 ppm. In addition, the colony showed respiratory problems with weight loss with recovery and related marked cannibalism, and pup death due to maternal death. The material tested appeared to be reasonably pure from acid equivalent measurements, but since no units were reported, this cannot be verified. The study was conducted prior to GLPs and the test material in the diet was not measured. Therefore the study is unacceptable/not upgradable.

N/L = NOAEL/LOAEL followed by effects at LOAEL unless otherwise specified; mkd = mg/kg/day. - = No study conducted or available; UA = Unacceptable study; UC = Unclassified study; a.i. = active ingredient. inc=increase; dec=decrease; histop=histopathology; DER= data evaluation record; neg=negative; pos=positive; Syst=systemic; HDT=highest dose tested; mod=moderate; Bwt=body weight; unoss=unossified; oss=ossification; M=maternal; D=developmental; UA=unacceptable; P=parental; Off=offspring; FOB=Functional Observation Battery; CARC=Cancer Assessment Review Committee.